5-22-2020

Increasing Distal-Proximal Temperature Gradient With Bed Socks to Improve Sleep in Analog Astronauts

Jessica Hockla
Yale Physician Associate Program, jessica.hockla@yale.edu

Increasing Distal-Proximal Temperature Gradient with Bed Socks To Improve Sleep in Analog Astronauts

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

May 2020

Jessica Hockla, PA-SII
Class of 2020
Yale Physician Associate Program

Lauren Tobias, MD Assistant Professor
Pulmonary, Critical Care, and Sleep
Medicine Yale School of Medicine

Table of Contents

Table of Figures

Abstract

Sleep quality and quantity in astronauts is a persistent problem, posing risks to mission success and crew safety. The prescription sleep aids used by astronauts to combat this issue have limited effectiveness. Furthermore, they may interfere with physical and cognitive function upon awakening, raising concerns about astronauts' ability to respond in emergency situations. There is a need for an alternative effective sleep intervention to improve sleep in astronauts. Increasing the distal-proximal temperature gradient by warming the extremities has been shown to improve sleep. Therefore, we propose a randomized, crossover trial investigating the use of bed socks worn at bedtime to increase the distal-proximal temperature gradient and improve sleep in analog astronauts in a simulated spaceflight environment versus controls. Our proposed intervention may provide a novel, effective means to improve sleep in astronauts without interfering with physical and cognitive function.

Chapter 1: Introduction

1.1 Background

Insomnia is a common issue, affecting between 10-15% of American adults.[1] These numbers are on the rise, with recent years demonstrating a seven-fold increase in individuals diagnosed with insomnia along with a corresponding 30-fold increase in prescriptions for nonbenzodiazepine sedative hypnotics.[1] While these statistics are striking, this issue is not limited to life only on our planet. A 10 year study found that crew members on the International Space Station allowed themselves less sleep opportunity, had shorter total sleep time, and had longer sleep latency during shuttle missions than on Earth.[2] While in flight, astronauts slept for less than six hours 47.1% of nights, with only 3% of all sleep episodes lasting eight hours or more. These statistics illustrate that astronauts sleep less despite using prescription sleep aids, a common countermeasure during spaceflight reported by approximately 75% of crewmembers.[2]

Astronauts and astronaut candidates are subjected to a range of factors that affect their ability to sleep. Time critical mission tasks frequently disrupt sleep schedules, requiring crew members to stay up late to prepare for the duties of the following day.[2] Crew members are also exposed to environmental factors that affect sleep schedule, duration, and quality. Noise is known to disrupt slow wave and REM sleep and is responsible for approximately 20% of reported sleep disturbances.[2] In flight, astronauts are subject to alterations in natural lighting compared to those experienced on Earth which may affect sleep quality.[2] Other environmental factors as well as psychological factors such as stress play a role as well.[2] While changes to sleeping quarters aimed to improve sleeping conditions have been

implemented on the International Space Station, control of some of these factors remains unattainable.

Sleep deficiency is known to increase the potential for human error and accidents.[2] These risks are of an increased concern in the harsh environment of space where error can place the lives of astronauts at risk. To combat the effects of insomnia in spaceflight, crew members frequently rely on prescription sleep aids[2]. Despite warnings by the United States Food and Drug Administration advising against the use of prescription sleep aids without a full night's sleep and while engaged in occupations requiring mental alertness and motor coordination, these drugs remain in use by personnel on board the International Space Station. For example, the commonly used sleep aids zolpidem and zaleplon have been shown to negatively impact performance in neurobehavioral testing during emergent awakening while the drugs were at maximal plasma concentration.[3] Considering that emergency alarms occur approximately six times per year on the International Space Station and that crew members must be capable of responding to these alarms at any time during their sleep cycle, these results are troubling.[3] Additionally, astronauts may overuse sleep aids, reporting that they take two doses of these medications approximately one out of six nights that they are used.[2] Furthermore, it is not clear that these medications are efficacious: in one study, average sleep efficiency increased by only 1.3%, with no improvement in sleep duration. Taken together, these findings indicate a need for more effective interventions to improve sleep of crew members without impairing performance.[2]

1.2 Statement of Problem

Sleep quality and quantity in astronauts during spaceflight is a persistent problem. Sleep deficiency is associated with an increased risk of error and accidents and deleterious

neurobehavioral effects.[2] Current interventions to improve sleep quality and quantity in astronauts frequently rely on the use of pharmacological sleep aids that have the potential to impact behavioral and cognitive performance upon emergent awakening, posing risks to crew health and safety.[2,3] Further, these pharmacological treatments have been shown to have little impact on sleep quality and quantity.[2] An effective intervention for improving sleep quality and quantity without impacting physical and mental performance is needed for use in the astronaut population.

1.3 Goals and Objectives

The goal of the proposed research is to investigate a novel, effective intervention to improve sleep in spaceflight. Specifically, we will examine the effect of the use of bed socks worn at bedtime on the distal-proximal temperature gradient and sleep quality and quantity in analog astronauts in a simulated spaceflight environment versus controls. We will evaluate the following outcomes: mean sleep latency, total sleep time, sleep efficiency, and number of awakenings. We will also examine secondary outcomes of mean distal-proximal temperature gradient and subjective measures of sleep quality and quantity and sleepiness.

1.4 Hypothesis

We hypothesize that bed socks applied to the feet at bedtime will increase the distal-proximal temperature gradient and improve sleep quality and quantity in analog astronauts in a simulated spaceflight environment versus controls. Among our primary outcomes, we expect to see a reduction in both mean sleep latency and number of awakenings and an increase in mean distal-proximal temperature gradient, total sleep time, and sleep

efficiency in the intervention group versus controls. In regards to our secondary outcomes, an increase in the distal-proximal temperature gradient and improved outcomes of subjective measures of sleep quality and quantity and sleepiness are expected in the intervention group versus controls.

1.5 Definitions

Distal-proximal temperature gradient: temperature difference between the skin of the torso and the skin of the extremities. Calculated by subtracting the proximal from the distal skin temperature, as measured by skin temperature sensor.

Sleep latency: the length of time from lights out to sleep onset, as measured by actigraphy.

Total sleep time: total time spent asleep, as measured by actigraphy.

Sleep efficiency: percentage of time spent asleep after lights out, as measured by actigraphy. Equivalent to the total time spent asleep divided by the total time in bed after lights out.

Number of awakenings: number of awakenings after sleep onset, as measured by actigraphy. An awakening is defined as an interruption of sleep >15 seconds.

Bed socks: Soft, fuzzy socks thicker than those used for wear with shoes and commonly worn in the home or to bed (see Figure 1).

Figure 1. Bed socks[4]

1.6 References

1. Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National use of prescription medications for insomnia: NHANES 1999-2010. *Sleep.* 2014;37(2):343-349.
2. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: AN observational study. *Lancet Neurol.* 2014;13(9):904-912.
3. Dinges DF, Basner M, Ecker AJ, Baskin P, Johnston S. Effects of Zolpidem and Zaleplon on Cognitive Performance After Emergent Tmax and Morning Awakenings: a Randomized Placebo-Controlled Trial. *Sleep.* 2018.
4. Gloutique. HASLRA Premium Soft Warm Microfiber Fuzzy Socks 3-5 Pairs. https://gloutique.com/product/haslra-stripe-soft-warm-microfiber-fuzzy-socks-5-pairs-stripe/. Accessed December 17, 2019.

Chapter 2: Review of the Literature

2.1 Introduction

Searches were made using PubMed, Ovid, Cochrane, Scopus, UpToDate, and the National Aeronautics and Space Administration website between July 2019 and December 2019. Various combinations of keywords and mesh terms were used including "astronaut," "cosmonaut," "space," "spaceflight," "Mir," "International Space Station," "shuttle," "NASA," "National Aeronautics and Space Administration," "SpaceX," "HERA," "simulation," "analog astronaut," "microgravity," "gravity," "orbit," "sleep," "circadian rhythm," "circadian misalignment," "fatigue," "zolpidem," "zaleplon," "hypnotics," "distal proximal temperature gradient," "skin temperature," "thermoregulation," "extremities," "foot," "hand," "proximal," "distal," "actigraphy," "polysomnography," "sensor," "thermistor" "iButton," "devices," "comparison," "crossover," "crossover design," and "crossover study."

2.2 Review of Empirical Studies

2.2.1 Factors Affecting Sleep in Astronauts and Interventions

A variety of factors have been shown to affect astronauts' sleep. Environmental conditions within sleeping quarters such as ambient temperature, noise levels, and bedding may cause problems with sleep.[5] In addition to the physical environment, astronauts' sleep is impacted by the varying schedule of mission activities they must accommodate in spaceflight as dictated by orbital mechanics and time zones on Earth.[6] Astronauts are also exposed to a marked alteration in light cycles, experiencing 90 minute light/dark cycles as they orbit Earth, in addition to artificial light aboard shuttle craft and the International Space

Station.[5,7,8] Both the lighting conditions and the schedules experienced by astronauts can cause circadian misalignment. [9] Data from 21 missions aboard the International Space Station showed circadian misalignment during 19% of sleep episodes, with increased likelihood of misalignment during operations including vehicle docking (23%) or extra-vehicular activities (29%).[9,10] Notably, the use of pharmacological sleep aids was significantly higher during periods of circadian misaligned sleep episodes (24%) vs. aligned sleep episodes (11%).[10] The microgravity experienced by astronauts in space may also lead to a change in the proprioceptive cues normally experienced on Earth and may influence the homeostatic regulation of sleep.[5] Additionally, psychological factors such as depression, anxiety, personality changes, crew conflicts, isolation and confinement, and stresses associated with spaceflight can contribute to sleep disturbance.[5,7,8]

Research has explored various countermeasures against these factors involved in astronauts' sleep disruption. On board the International Space Station, improvements were made to astronauts' sleep quarters to reduce noise and regulate ambient temperature.[5] Design changes were made to increase the comfort of sleeping bags as well as to implement restraints to reduce floating.[5] Astronauts were also given private sleeping quarters, an improvement over previous sleeping arrangements.[5] Improvements to lighting have been implemented on the International Space Station as well, providing a dynamic lighting schedule utilizing varied wavelengths throughout the day to promote alertness or sleep through use of white or blue light.[11] Under the guidance of flight surgeons, flight schedules have been adjusted to minimize disruptions to astronaut sleep.[11] Cognitive behavioral therapy, the standard of care for treatment of insomnia on Earth, has also been investigated in astronauts.[5] Despite these interventions, astronauts continue to rely regularly on the use

of pharmacological sleep aids. While these drugs are intended to be a last resort to promote sleep, approximately 75% of astronauts report use.[2] The most commonly used medications are zolpidem and zaleplon.[2,5,12] These medications, particularly zolpidem, have been shown to negatively affect behavioral and cognitive outcomes upon emergent awakening when the drugs are at maximal plasma concentrations, posing potential risks to crew safety.[3]

2.2.2 Role of the Distal-Proximal Temperature Gradient in Sleep

The distal-proximal temperature gradient is defined as the difference in temperature between the skin of the extremities and the skin of the torso. During wakefulness, the distal-proximal temperature gradient is approximately -2.5℃, meaning that the proximal skin temperature is 2.5℃ higher than the distal skin temperature.[13] As the body prepares for sleep, the distal temperature rises as the proximal temperature drops until these values are approximately equal at the time of sleep onset, resulting in a distal-proximal temperature gradient approaching 0℃.[13] Increases in the distal-proximal temperature gradient positively correlate with the degree of blood flow in the distal extremities, providing an indirect measure of heat loss in these areas.[14] This phenomenon is regulated by the body's circadian rhythm.[14] Vasodilation of the extremities begins in the evening as the body prepares to sleep, resulting in a drop of core body temperature.[14] The degree of distal vasodilation, measured via the distal-proximal temperature gradient, has demonstrated application in predicting sleep patterns.[14] In infants and school age children, an increase in the distal-proximal temperature gradient is a reliable indicator of impending sleep.[15,16] Similar findings have been seen in adults, where an increased distal-proximal temperature gradient correlates with decreased sleep latency.[14]

Several studies have shown that heat application to the periocular area or to the extremities can be utilized to increase the distal-proximal temperature gradient and influence sleep. A crossover study by Ichiba et al. demonstrated that heat application to the periocular skin using a heat- and steam-generating eye mask resulted in an increase of the distal-proximal temperature gradient between the skin of the hand and the skin of the torso as well as between the skin of the foot and the skin of the torso, versus no changes in the distal-proximal temperature gradient seen in a sham eye mask in healthy male subjects (29-57 years old, n=20).[17] This technique of periocular warming resulted in temperature increases selectively in the skin of the hands and feet, not the core or skin, thereby resulting in an increase in the distal-proximal temperature gradient.[17] Participants demonstrated significant increases in subjective sleepiness, as measured by the Karolinska Sleepiness Scale, 50 minutes after application of the eye mask.[17] No significant differences in sleepiness were observed in subjects when wearing the sham eye mask.[17]

Sung and Tochihara investigated the effects of a footbath before bedtime on sleep in healthy female subjects (21-40 years old, n=9) versus controls.[18] Outcomes including total sleep time, sleep efficiency, sleep latency, and wake time after sleep onset were measured using data from polysomnography and subjective sleep outcomes of sleepiness, sleep maintenance, anxiety, synthetic sleep, and falling asleep were measured using the Oguri-Shirakawa-Azumi sleep questionnaire.[18] Subjects in the footbath treatment group received a footbath for 30 minutes immediately prior to lights out.[18] Mean sleep latency was significantly decreased in the footbath group versus the control group (no intervention) (15.50 vs. 29.39 minutes, $p<0.05$).[18] They observed increases in mean sleep efficiency (93.77 vs. 90.34%) and total sleep time (393.83 vs. 379.39 minutes) and a decrease in wake

time after sleep onset (10.67 vs. 11.17 minutes) in the footbath group versus the control group, but these results were not significant.[18] However, subjective sleep outcome scores using the Oguri-Shirakawa-Azumi sleep questionnaire were significantly increased in the footbath group versus the control group (864.0 vs. 600.0, $p<0.05$), with increasing scores correlating with improved sleep outcomes.[18]

A crossover study by Liao et al. showed that a warm footbath can be used to increase the distal-proximal temperature gradient in older adults (60-73 years).[19] A second crossover study conducted by Liao et al. used polysomnography and subjective measures of sleep quality (Morning Questionnaire) to determine sleep outcomes in older adults (60-75 years, n=15) with self-reported sleep difficulties treated with a warm footbath an hour prior to bedtime versus controls.[20] The distal-proximal temperature gradient was significantly increased after receiving a footbath (mean distal-proximal temperature gradient of -3.11℃ and -0.81℃ before and after footbath, respectively).[20] Although polysomnography revealed less wakefulness in the second stage of REM sleep after receiving a footbath versus controls, no other significant differences in objective or subjective ratings of sleep were seen.[20] The authors noted the discrepancies between their results and those of prior studies using passive body heating showing improved sleep outcomes, citing the possibility of confounding due to decreased heat dissipation capacity in older adults, ambient temperature (as the study was conducted in the summer), timing of the footbath relative to bedtime, and elevation of the core temperature in addition to the skin temperature.[20]

Oshima-Saeki, et al. conducted a prospective cohort study examining the effects of heat packs applied to the lower limbs on the sleep quality and quantity of elderly female subjects (74-93 years old, n=7) living in a nursing home.[21] Subjects received a 40 minute heat pack

treatment prior to bed daily for eight weeks. Outcomes of sleep latency, total sleep time, duration of long-sleep episode, wake episodes after sleep onset, and sleep efficiency were calculated using data collected via actigraphy.[21] Measurements were made once one week prior to starting the intervention (week one) and repeated after eight weeks of receiving the heat pack treatments (week nine).[21] There was a significant decrease in median sleep latency (11.25 vs. 47 minutes, p=0.043) and wake episodes after sleep onset (9 vs. 10.67 awakenings, p=0.018) at week nine versus week one.[21] There was also a decrease in median total sleep time (392.75 vs. 409.75 minutes) and an increase in duration of long-sleep episode (105.5 vs. 99.6 minutes) and sleep efficiency (80.95% vs. 77.37%) at week nine versus week one, but these differences were not statistically significant.[21]

Ko and Lee conducted a crossover trial investigating the effects of passive heating through the use of bed socks applied an hour prior to lights out and worn for the duration of sleep on the sleep of young male subjects (mean age of 22.7 years, n=6) versus controls.[22] Outcomes including sleep latency, sleep efficiency, total sleep time, and number of awakenings were calculated using data collected via actigraphy.[22] Subjective sleep measures including movement during sleep, depth of sleep, feeling of rest upon awakening, spontaneity of wakening in the morning, and general ratings of sleep satisfaction, quality, and disturbance were made using a questionnaire designed by the authors.[22] Calculations of the distal-proximal temperature gradient were made using data collected via skin temperature probes recorded automatically using a data logger.[22] The average distal-proximal temperature gradient was significantly higher in the treatment than the control group (-0.19℃ vs. -0.78℃).[22] There was a significant decrease in mean sleep latency (8.5 vs. 16 minutes, p=0.018) and number of awakenings (8.8 vs. 16.3 awakenings, p=0.041)

and a significant increase in mean sleep efficiency (93.8 vs. 86.2%, p=0.047) and total sleep time (394.0 vs. 362.0 minutes, p=0.047) in treatment versus control groups.[22] While subjective sleep measures showed a trend toward improvement with bed socks, these differences were not statistically significant.[22]

Several factors must be considered when evaluating the above studies. The nature of the interventions employed to increase the distal-proximal temperature gradient varied across studies, which may have impacted the observed outcomes. For example, the degree of heat applied to the extremities ranged from passive warming with bed socks (average skin temperature of 35℃) to heat sources providing a minimum of 38℃ to a maximum of 42℃.[17,18,20-22] There was also variation in the ambient temperature of the facilities where the experiments occurred. Four of the studies utilized ambient temperatures ranging from 21-28℃, while the study by Sung and Tochihara used and ambient temperature of 10℃.[17,18,20-22] These variations of both the degree of applied heat and the ambient temperature may have confounded results. Participant age also varied widely across studies, ranging from 21 to 93 years old.[17,18,20-22] There are known baseline differences in sleep quality and quantity between younger patients and the elderly, possibly introducing confounding.[17,18,20-22] Furthermore, since vasodilation was postulated to mediate the experimental relationship in these studies, it is possible that age-related circulatory changes led to differences in outcomes between age groups, given the higher rates of circulation problems in the elderly.[17,18,20-22] While each of the studies yielded significant results, the sample sizes used were small, ranging from six to 20.[17,18,20-22] Several studies showed trends toward improvements in sleep outcomes that failed to reach significance, perhaps owing to insufficient sample size.[18,21,22] Finally, the nature of the interventions used in these

studies precluded participant blinding of treatment groups. While Ichiba et al. used a sham eye mask in their study, they note that study subjects were able to discern the sham from the treatment eye mask due to the warming effect of the intervention.[17] None of the remaining studies attempted blinding of subjects, introducing a potential source of bias. [17,19-21]

2.2.3 Review of Studies to Identify Possible Confounding Variables

A review of prior studies investigating the relationship between distal-proximal temperature gradient and sleep exposes a number of confounding variables. Baseline characteristics such as sleep disorders, sleep disturbance, irregular sleep patterns, use of hypnotic medication, sleep apnea, acute illness, diabetes, peripheral vascular disease, and major mental disorders were used as exclusion criteria for a number of studies.[17,20-23] Age was also noted as a potential confounder.[20]

Dietary factors such as caffeine use, diet composition, and time of last meal prior to bedtime were controlled or kept consistent between the arms of studies to limit their effects on sleep.[17,22,23] Activity levels were also kept consistent throughout study periods and subjects were instructed to avoid heavy exercise.[22]

Environmental factors such as ambient temperature, light levels, and noise may also confound results.[17,21-23] Efforts to keep these variables consistent between study groups were made in several studies.[17,21-23] Bedding and clothing were also kept consistent between study groups in prior research.[22] Posture is also known to affect the distal-proximal temperature gradient and previous studies used a constant routine protocol to standardize postural conditions prior to lights out to account for this factor.[17,23]

Variations in individual sleep schedules were also cited in past research as a potential confounder. [17,20-23] Some studies used run-in periods to normalize sleep schedules before the start of data collection, requiring participants to sleep at designated times leading up to the beginning of the study, while other researchers collected observational sleep data during the time period before the study to identify participants with irregular sleep schedules at baseline.[17,20-23]

Carryover effects are a potential confounder in trials with crossover design, as will be utilized in our trial.[3,24] We plan to employ a common strategy to minimize such confounding with the use of washout periods between different interventions.[3,22,24]

2.3 Review of Relevant Methodology

2.3.1 Human Exploration Research Analog Facility and Analog Astronauts

Through its Human Research Program, the National Aeronautics and Space Administration (NASA) funds internal and external research with the objectives of assessing effects of long-duration spaceflight on humans, developing and verifying methods enabling optimal crew performance, and engineering and assessing a variety of physical, pharmacological, and nutritional interventions to protect the health and performance of crew members.[25] Research associated with the Human Research Program occurs in one of three environments: “flight,” conducted on the International Space Station; “analog,” using NASA spaceflight analog facilities; or “ground-based,” which does not involve flight or analog facilities.[26] While the ideal study of a treatment for application to astronauts in spaceflight would take place on the International Space Station, the feasibility of this is limited by a number of factors including cost, availability of subjects, and the two year

time frame for all recruitment and data collection dictated as an institutional requirement for this Yale Physician Associate Program thesis. According to guidelines published by NASA, all recruitment of astronauts for human research conducted on the International Space Station occurs a year prior to launch, leaving only a year for data collection in the case of the research we propose here.[27] These guidelines also state that the maximum number of human subjects per year is six although investigators should plan on four participants for a conservative estimate when calculating the sample size necessary for their research.[27] Based on these guidelines and the two year time limit imposed on this thesis, conducting our study aboard the International Space Station will not afford an adequate sample size. Therefore, we propose using the NASA Human Exploration Research Analog (HERA) facility located at Johnson Space Center as a substitute for the environment of the International Space Station. HERA is a two-story, four-port, 148.1 m^3 closed habitat analog facility designed to simulate conditions associated with spaceflight such as isolation, confinement, and remote conditions.[28] It consists of a core, loft, airlock, and hygiene module as depicted in Figures 2-4.

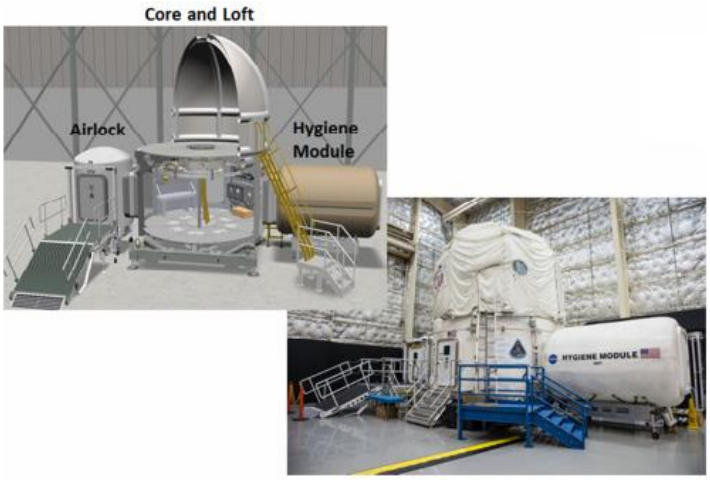


Figure 2. HERA facility[27]

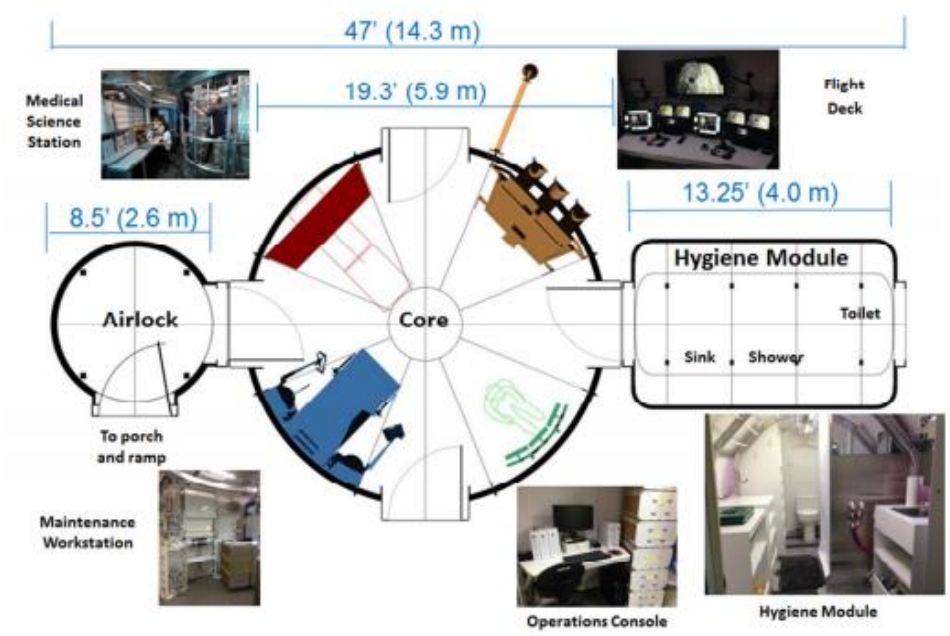


Figure 3. HERA first level[27]

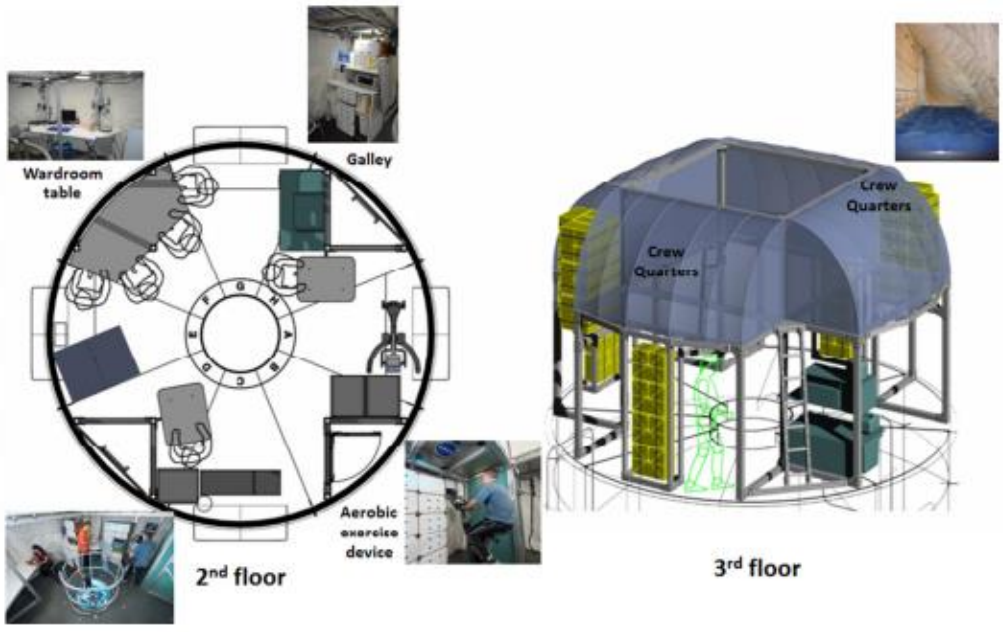


Figure 4. HERA second and third levels[27]

Participants are quarantined to the facility for the duration of the study and are not permitted access to email, phone, or internet. The HERA facility has a network that allows voice communication with ground controllers and access to electronic research data during the mission as well as a surveillance video and audio system. The facility is equipped with actigraphy, laptops, and iPads for investigator data collection.[29] While in HERA, participants are subjected to schedules and tasks similar to those experienced by astronauts on the International Space Station [see Appendix A].[29] Conditions are standardized in the HERA facility and include a room temperature of 72°F (+/- 5°F), a light/dark cycle with lights on at 7am and lights off at 11pm seven days per week with no napping allowed, and three meals per day.[29]

This facility is available for use by researchers external to NASA pending a proposal process. HERA has been used for prior studies examining sleep quality in astronauts, making this an ideal location to conduct our proposed research.[30] Further, the increased availability of research subjects (up to 32 per study) allows for a sample size that we anticipate will be large enough to demonstrate significant results based on the effect sizes of outcomes of past research.[22]

HERA is structured such that four study subjects participate in each 45-day mission.[27] There are four missions per year, and investigators may conduct research over the span of up to two years, or eight missions, for a total of 32 subjects.[27] Experimental conditions are kept standard during this time period, referred to as a campaign, to ensure consistency between individual missions.[27] Each campaign involves multiple investigations by different researchers to maximize resources.[27] To facilitate this process, the following set

of services, quoted here from the HERA Experiment Information Package, is provided by the Flight Analogs Team at Johnson Space Center:

- *"Coordinate investigator meetings*
- *Coordinate preparation and submissions to the Johnson Space Center Institutional Review Board*
- *Recruit and perform standard subject screening through the JSC Test Subject Screening facility, subject reimbursement, and transport*
- *Provide monitors and coordinators to oversee study operations*
- *Provide medical monitors through the Test Subject Screening facility when needed*
- *Develop and manage schedules and the associated logistics to implement integrated studies*
- *Enable the capability to transfer electronic data from HERA to remote investigators via the Telescience Center*
- *Coordinate logistics for shipment of investigator equipment*
- *Receive investigator hardware shipment and coordinate with the investigator for setup and checkout of their hardware*
- *Provide test subject and medical staff orientations*
- *Conduct integrated Test Readiness Reviews, safety walk-throughs and operations check-outs prior to starting the study*
- *Provide a daily operational status report*
- *Coordinate post-study subject follow up testing if required"*[27]

Principal investigators using the HERA facility have responsibilities according to the guidelines set forth in the HERA Experiment Information Package as quoted below:

- *"Meet with Flight Analogs Team and investigators of other studies to develop integrated protocols*
- *Ensure that investigator study requirements are compatible with the standard conditions of HERA to the degree that this is possible without compromising scientific results*
- *Provide for on-site study support at the HERA facility at Johnson Space Center, Houston, TX including investigator resources and scientific expertise*
- *Budget for costs associated with on-site support*
- *Carry out investigator science according to protocols with integrity and professionalism*
- *Participate in periodic data debriefs*
- *Provide complete experimental data sets to the NASA Life Sciences Data Archive*
- *Provide manuscript(s) within 2 years of study completion for inclusion into the final project report*

INVESTIGATOR PREPARATIONS FOR HUMAN SUBJECTS BOARDS:

- *Work with the Flight Analogs team to determine needed approvals from the investigator's home institution*
- *Prepare individual protocol submissions with the assistance of Flight Analogs team to the Johnson Space Center Institutional Review Board*

INVESTIGATOR RESOURCE/FISCAL RESPONSIBILITIES:

- *The investigator will provide resources for their experiment unique requirements*
- *Provide subject consent briefings for the specific study*
- *The investigator will have responsibility for the costs of any investigator protocol specific screening requirements, equipment, and other investigation-specific requirements*
- *The investigator is responsible for costs associated with his specific protocol operations*
- *The investigator is responsible for test subject travel costs for follow up testing required beyond the standard schedule"* [27]

Our study and planned implementation are designed to meet these guidelines.

2.3.2 Patient Recruitment

NASA has a continuous call for analog astronaut applicants advertised on its website. Multiple studies are conducted simultaneously during each HERA mission using the same group of analog astronauts. All research conducted using the HERA facility utilizes the individuals selected by NASA in accordance with guidelines that aim to recruit individuals with physical and mental characteristics similar to those of astronaut candidates.[31] Our research will follow this patient recruitment process required for use of the HERA facility.

2.3.3 Inclusion and Exclusion Criteria

Study participants will be selected by NASA according to the inclusion criteria for individuals participating in HERA missions which include an age of 26-55 years, a height limit of 6'2", experience demonstrating technical skills including an advanced degree or

equivalent experience, demonstrated motivation and work ethic, and the ability to pass the NASA long-duration spaceflight physical which includes the criteria of visual acuity correctable to 20/20 in both eyes and a maximum blood pressure of 140/90 in a sitting position.[27]

Our study will utilize the analog astronauts selected by NASA for each HERA mission included in our study and thus our study participants will meet the above inclusion criteria. Additional participant requirements set by our research reflect the confounding baseline characteristics mentioned in previous studies and will exclude individuals with preexisting sleep problems, sleep apnea, usage of hypnotic medication, diabetes, acute illness, peripheral vascular disease, and major mental disorders.[17,20-23]

2.3.4 Crossover Design

Crossover designs were used in numerous previous studies investigating the relationship between distal-proximal temperature gradient and sleep.[17,18,20-22] Crossover studies have several advantages over parallel group trials. First, crossover studies require smaller sample size.[32] This is of importance in our study considering its limitation to four subjects per mission, with a total of 32 subjects available for our investigation. A second advantage to the crossover design is the elimination of between-patient variation since each subject acts as his or her own control.[32] This is important to account for variations in the sleep habits of different individuals in our research, a confounder identified by previous studies. [17,20-23]

2.3.5 Data Collection

Actigraphy has been validated as a reliable estimator of sleep parameters.[33] Many previous studies investigating the relationship between the distal-proximal temperature gradient and

sleep utilized actigraphy for data collection, and this is a commonly utilized method across sleep research.[21,22,33,34] While polysomnography is considered the "gold standard" for measurements of sleep, it has limitations applicable to our study. The isolation conditions of the HERA facility preclude the possibility of a researcher setting up nightly polysomnography, which requires placement of multiple electrodes and sensors. Further, patients may have difficulty sleeping due to discomfort related to equipment which may present issues due to the fact that our research involves multiple nights of data collection.[35] Actigraphy has been used successfully in prior research investigating sleep in analog astronauts as well as astronauts in spaceflight.[3,36,37] These considerations have guided our choice of actigraphy as a method of data collection for objective sleep outcomes. One limitation cited in the literature is the accuracy of actigraphy in calculating sleep latency.[33] Martin and Hakim recommend corroborating sleep latency using subjective information from a sleep diary.[33] We plan on incorporating this method into our study. We will be using the Philips Actiwatch Spectrum PRO *(Philips Respironics)*, the actigraphy equipment provided for use in the HERA facility, for data collection in our study.[29]

Data collection for the calculation of the distal-proximal temperature gradient will be done by skin temperature sensor. We have chosen the Thermochron iButton *(Maxim Integrated)*, a temperature sensor that has demonstrated reliability and has been used in multiple studies investigating skin temperature in sleep-wake cycles.[24,38-44] The benefits of this device include easy application using medical adhesive tape, subject comfort during wear, years of battery life, and a wireless design, factors that are important to our study considering the isolation of subjects in the HERA facility and the duration of the study.[38] We will utilize the same methodology for the placement of the iButton devices on the skin and for the

calculation of the distal-proximal temperature gradient used by prior investigators.[22] iButtons will be placed on the forehead, chest, abdomen, hand, thigh, and foot.[22] Temperature will be monitored continuously throughout the night at 30 second sampling intervals, as done in prior studies.[22] The proximal temperature will be calculated as the mean skin temperature of the chest, thigh, abdomen, and forehead, while the distal temperature will be calculated as the mean skin temperature of the hand and foot. The distal-proximal temperature gradient will be calculated by subtracting the proximal from the distal temperature.[22]

Subjective measures of sleep outcomes and sleepiness will be conducted using daily sleep questionnaires. We will create a questionnaire [see Appendix B] applicable to our study using content based on the Pittsburgh Sleep Quality Index and the Karolinska Sleepiness Scale, validated and commonly used subjective measures of sleep quality and sleepiness.[45,46]

2.3.6 Choice of Intervention

Ko and Lee demonstrated an increased distal-proximal temperature gradient and improved outcomes of mean sleep latency, sleep efficiency, total nightly awakenings, and total sleep time in healthy men wearing bed socks to bed versus controls.[22] Among the studies investigating various methods of increasing the distal-proximal temperature gradient and evaluating its effects on sleep, the study by Ko and Lee yielded improvement in the largest number of sleep outcomes, showing promise for the use of bed socks in applications for improving sleep and guiding our choice to this intervention for our proposed study.[17,20-22] Another consideration in our selection of this intervention is the age group of the patients in this study. Several of the other interventions in the literature were conducted on the

elderly, while our study participants will range from 30-55 years old. Given the known differences in sleep between younger individuals and the elderly, we wanted to choose an intervention that had demonstrated success in the age group of our study subjects. Further, the ambient temperature used in the study by Ko and Lee was 23℃ which falls close to the 72°F (22.22℃) ambient temperature in the HERA facility.[22]

While our proposed research will be conducted in the HERA simulation facility, the motivation behind our study is to develop an intervention suitable for use in astronauts in spaceflight. An important consideration, therefore, is the feasibility of the use of our intervention in space. The cost of sending 1 kg of cargo into orbit is approximately $20,000 USD via SpaceX's Dragon cargo spaceship that is used to resupply the International Space Station.[47] Therefore, the mass of the materials required for the intervention is a significant factor. Other research used heat packs, footbaths, and disposable eye masks. [17,20-22] The materials required for each of these interventions have more mass than our intervention requiring only bed socks. Additional complications associated with using other methods from the literature include the issues associated with using a footbath in microgravity, the impracticality of warming heat packs nightly, and the constant need for resupply and disposal with disposable eye masks.

Our choice to use bed socks as a primary intervention was guided by these factors of sleep outcomes, population, environmental conditions, and applicability of our intervention to spaceflight.

2.3.7 Outcome Measures

Studies using actigraphy for data collection regarding sleep quality and quantity share similarities in the measures of objective sleep outcomes.[22,48-51] Total sleep time is defined as the total time spent asleep and is consistently reported outcome.[22,48-51] Sleep latency, also referred to as sleep onset or sleep onset latency, is another frequently reported outcome that is defined as the time period between lights out and sleep onset. [22,48-51] Many studies also include a measure reflecting either the time spent awake after sleep onset or the number of awakenings after sleep onset.[22,48-51] These outcomes were reported in various ways including the number of total nightly awakenings, defined as the number of arousals >15 seconds after sleep onset; wakefulness after sleep onset, defined as the time spent awake after sleep onset; and awakening index, defined as the ratio of number of awakenings after sleep onset to the total sleep time in hours.[22,48-51] Sleep efficiency is another outcome often seen in the literature, and is defined as the ratio of time spent asleep to the time spent in bed, expressed as a percentage.[22,48-51]

In our study, we have chosen to use objective sleep outcomes of total sleep time, sleep latency, number of awakenings, and sleep efficiency. Our choice of outcome measures reflects both what is found in the literature as well as the outcomes used in the study by Ko and Lee whose intervention is most closely reflected in our research.[22]

Subjective measures of sleep and daytime sleepiness are also commonly reported in the literature.[10,17,22-24,33,45,46,52] We have chosen to use content from the Pittsburgh Sleep Quality Index and the Karolinska Sleepiness Scale, two validated subjective measures of sleep and sleepiness, as a basis to create a questionnaire [Appendix B] to be completed daily by participants in our research.[45,46]

2.4 Conclusion

Several studies have investigated interventions to increase the distal-proximal temperature gradient to improve sleep quality and quantity in healthy young subjects and in the elderly.[17,18,20-22] Among these studies, research by Ko and Lee utilizing passive warming of the feet using bed socks worn at bedtime demonstrated improvement of the largest number of sleep outcomes including sleep latency, total sleep time, sleep efficiency, and number of awakenings in healthy young men.[22] Our proposed study will be the first to examine the effect of bed socks worn at bedtime on sleep outcomes in analog astronauts in the HERA facility, a simulated spaceflight environment used by NASA for research with potential generalizability to spaceflight.[27] Our study may provide evidence supporting a novel, inexpensive, and safe method to improve sleep quality and quantity in astronauts.

2.5 References

2. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: AN observational study. *Lancet Neurol.* 2014;13(9):904-912.
3. Dinges DF, Basner M, Ecker AJ, Baskin P, Johnston S. Effects of Zolpidem and Zaleplon on Cognitive Performance After Emergent Tmax and Morning Awakenings: a Randomized Placebo-Controlled Trial. *Sleep.* 2018.
5. Wu B, Wang Y, Wu X, Liu D, Xu D, Wang F. On-orbit sleep problems of astronauts and countermeasures. *Military Medical Research.* 2018;5(1):17.
6. Whitmire A, Leveton L, Barger L, et al. Risk of Performance Errors Due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload Risk of Performance Errors due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload. *Evidence-Based Review by NASA Behavioral Health and Performance Program.* 2009.
7. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *The Lancet Neurology.* 2014;13(9):904-912.
8. Pandi-Perumal SR, Gonfalone AA. Sleep in space as a new medical frontier: the challenge of preserving normal sleep in the abnormal environment of space missions. *Sleep science (Sao Paulo, Brazil).* 2016;9(1):1-4.

9. Brainard GC, Barger LK, Soler RR, Hanifin JP. The development of lighting countermeasures for sleep disruption and circadian misalignment during spaceflight. *Curr Opin Pulm Med.* 2016;22(6):535-544.
10. Flynn-Evans EE, Barger LK, Kubey AA, Sullivan JP, Czeisler CA. Circadian misalignment affects sleep and medication use before and during spaceflight. *npj Microgravity.* 2016;2.
11. Gregory K. *Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload.* 2016.
12. Wotring VE. Medication use by U.S. Crewmembers on the International space station. *FASEB J.* 2015;29(11):4417-4423.
13. Troynikov O, Watson CG, Nawaz N. Sleep environments and sleep physiology: A review. *J Therm Biol.* 2018;78:192-203.
14. Krauchi K, Cajochen C, Werth E, Wirz-Justice A. Warm feet promote the rapid onset of sleep. *Nature.* 1999;401(6748):36-37.
15. Abe N, Kodama H. Distal-proximal skin temperature gradient prior to sleep onset in infants for clinical use. *Pediatr Int.* 2015;57(2):227-233.
16. McCabe SM, Elliott C, Langdon K, Abbiss CR. Patterns and reliability of children's skin temperature prior to and during sleep in the home setting. *Physiology & behavior.* 2018;194:292-301.
17. Ichiba T, Suzuki M, Aritake-Okada S, Uchiyama M. Periocular skin warming elevates the distal skin temperature without affecting the proximal or core body temperature. *Scientific reports.* 2019;9(1):5743.
18. Sung EJ, Tochihara Y. Effects of bathing and hot footbath on sleep in winter. *Journal of physiological anthropology and applied human science.* 2000;19(1):21-27.
19. Liao WC, Landis CA, Lentz MJ, Chiu MJ. Effect of foot bathing on distal-proximal skin temperature gradient in elders. *International journal of nursing studies.* 2005;42(7):717-722.
20. Liao WC, Chiu MJ, Landis CA. A warm footbath before bedtime and sleep in older Taiwanese with sleep disturbance. *Research in nursing & health.* 2008;31(5):514-528.
21. Oshima-Saeki C, Taniho Y, Arita H, Fujimoto E. Lower-limb warming improves sleep quality in elderly people living in nursing homes. *Sleep Sci.* 2017;10(2):87-91.
22. Ko Y, Lee JY. Effects of feet warming using bed socks on sleep quality and thermoregulatory responses in a cool environment. *J Physiol Anthropol.* 2018;37(1):13.
23. Krauchi K, Cajochen C, Wirz-Justice A. Waking up properly: is there a role of thermoregulation in sleep inertia? *Journal of sleep research.* 2004;13(2):121-127.
24. Dorsey CM, Lukas SE, Teicher MH, et al. Effects of passive body heating on the sleep of older female insomniacs. *Journal of geriatric psychiatry and neurology.* 1996;9(2):83-90.
25. NASA. Human Research Program: About International Space Station Medical Projects. https://www.nasa.gov/hrp/elements/issmp/about. Published 2018. Accessed 7/12, 2019.

26. NASA. Human Exploration Research Opportunities (HERO). In:2017.
27. NASA SM. Human Research Program Flight Experiment Information Package. In: Projects ISSM, ed2019.
28. NASA. Analog Missions. https://www.nasa.gov/analogs/hera. Published 2019. Accessed 7/13, 2019.
29. NASA. Human Research Program Human Exploration Research Analog (HERA) Experiment Information Package. In: Program HR, ed2014.
30. NASA. Analog Missions: HERA Research by Campaign. https://www.nasa.gov/analogs/hera/research. Published 2019. Accessed 7/13, 2019.
31. NASA. Analog Missions: Want to Participate in HERA? https://www.nasa.gov/analogs/hera/want-to-participate. Published 2018. Accessed 7/13, 2019.
32. Stoner J. Cross-Over Trials in Clinical Research (2nd ed.) by Stephen Senn. *Journal of the American Statistical Association.* 2004;99.
33. Martin JL, Hakim AD. Wrist actigraphy. *Chest.* 2011;139(6):1514-1527.
34. Izmailova ES, McLean IL, Bhatia G, et al. Evaluation of Wearable Digital Devices in a Phase I Clinical Trial. *Clin Transl Sci.* 2019;12(3):247-256.
35. Kramer NaM, R. Overview of polysomnography in adults. UpToDate. Published 2018. Updated September 11, 2018. Accessed December 13, 2019.
36. Monk TH, Buysse DJ, Rose LR. Wrist actigraphic measures of sleep in space. *Sleep.* 1999;22(7):948-954.
37. Basner M, Dinges DF, Mollicone D, et al. Mars 520-d mission simulation reveals protracted crew hypokinesis and alterations of sleep duration and timing. *Proceedings of the National Academy of Sciences of the United States of America.* 2013;110(7):2635-2640.
38. Hasselberg MJ, McMahon J, Parker K. The validity, reliability, and utility of the iButton(R) for measurement of body temperature circadian rhythms in sleep/wake research. *Sleep medicine.* 2013;14(1):5-11.
39. van Marken Lichtenbelt WD, Daanen HA, Wouters L, et al. Evaluation of wireless determination of skin temperature using iButtons. *Physiology & behavior.* 2006;88(4-5):489-497.
40. Smith AD, Crabtree DR, Bilzon JL, Walsh NP. The validity of wireless iButtons and thermistors for human skin temperature measurement. *Physiological measurement.* 2010;31(1):95-114.
41. Sarabia JA, Rol MA, Mendiola P, Madrid JA. Circadian rhythm of wrist temperature in normal-living subjects A candidate of new index of the circadian system. *Physiology & behavior.* 2008;95(4):570-580.
42. Rutkove SB, Nie R, Mitsa T, Nardin RA. A methodology for the real-time measurement of distal extremity temperature. *Physiological measurement.* 2007;28(11):1421-1428.
43. Raymann RJ, Swaab DF, Van Someren EJ. Cutaneous warming promotes sleep onset. *American journal of physiology Regulatory, integrative and comparative physiology.* 2005;288(6):R1589-1597.

44. Fronczek R, Raymann RJ, Romeijn N, et al. Manipulation of core body and skin temperature improves vigilance and maintenance of wakefulness in narcolepsy. *Sleep.* 2008;31(2):233-240.
45. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 1989;28(2):193-213.
46. Kaida K, Takahashi M, Akerstedt T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2006;117(7):1574-1581.
47. Mosher DaK, S. Here's how much money it actually costs to launch stuff into space. Business Insider. Published 2016. Accessed December 12, 2019.
48. Thurman SM, Wasylyshyn N, Roy H, et al. Individual differences in compliance and agreement for sleep logs and wrist actigraphy: A longitudinal study of naturalistic sleep in healthy adults. *PloS one.* 2018;13(1):e0191883-e0191883.
49. Taibi DM, Landis CA, Vitiello MV. Concordance of polysomnographic and actigraphic measurement of sleep and wake in older women with insomnia. *J Clin Sleep Med.* 2013;9(3):217-225.
50. Smith MT, McCrae CS, Cheung J, et al. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. *J Clin Sleep Med.* 2018;14(7):1209-1230.
51. Cellini N, Buman MP, McDevitt EA, Ricker AA, Mednick SC. Direct comparison of two actigraphy devices with polysomnographically recorded naps in healthy young adults. *Chronobiol Int.* 2013;30(5):691-698.
52. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. Before-bedtime passive body heating by warm shower or bath to improve sleep: A systematic review and meta-analysis. *Sleep medicine reviews.* 2019;46:124-135.

Chapter 3: Study Methods

3.1 Study Design

Our proposed study is a randomized, two-sequence, two-period, two-treatment, crossover trial of uniform design.

	Run-in (7 days)	Period 1 (15 days)	Washout (8 days)	Period 2 (15 days)
Sequence AB	No treatment	A	No treatment	B
Sequence BA	No treatment	B	No treatment	A

Figure 5. Study design. A=intervention (bed socks), B=no intervention (control group)

During each of the eight HERA missions in our study, subject participants will be randomly assigned to one the two treatment sequences via computer software in a 1:1 ratio.

The entire duration of participants' stay in the HERA facility will be 45 days. There will be a seven day run-in period in the HERA facility to acclimate participants to the environment and the light/dark cycle of lights off at 11pm and lights on at 7am. After this run-in period, participants will begin their assigned intervention for Period 1. Each period will consist of 15 days and participants will adhere to their assigned intervention daily for the entire duration. There will be an eight day washout period after Period 1, after which participants will begin Period 2 which will continue for the remaining 15 days of their stay in the HERA facility.

3.2 Study Variables and Measures

3.2.1 Independent Variable:

The independent variable (intervention) in our study will be the application of bed socks [Appendix C] to participants' feet prior to sleep. Socks will be put on the feet one hour

prior to lights out each night for the duration of the period the participant is assigned to receive the intervention. Socks will be removed when the participant gets out of bed in the morning.

3.2.2 Dependent Variables:

The primary dependent variables we will measure in this study are sleep latency, total sleep time, sleep efficiency, and number of awakenings, as measured via actigraphy. Sleep latency will be calculated as the time difference between lights out and the onset of sleep. Total sleep time will be calculated as the total time that a subject spends asleep. Sleep efficiency is the percentage of time spent asleep after lights out. This will be calculated by dividing the time a subject spends asleep by the duration of the time the subject spends in bed after lights out. Number of awakenings will be calculated as the total number of times a participant wakes up after lights out.

Other variables we will measure during our study are subjective perceptions of sleep quality and quantity and sleepiness, and the distal-proximal temperature gradient. Subjective perceptions of sleep quality and quantity and sleepiness will be assessed through the use of a questionnaire [see Appendix B]. The distal-proximal temperature gradient will be calculated as the mean distal temperature minus the mean proximal temperature, as measured via skin temperature sensor. The proximal temperature will be calculated as the mean skin temperature of the chest, thigh, abdomen, and forehead, while the distal temperature will be calculated as the mean skin temperature of the hand and foot.

3.3 Study Population and Sampling

Selection of our study population will be dictated by the guidelines set by the NASA Human Research Program. All advertising, recruitment, and screening of human test

subjects involved in HERA simulations is conducted through the NASA Johnson Space Center Test Subject Screening facility. These guidelines require four analog astronauts per mission, with a total of 32 participants over the course of the eight mission campaign. Other requirements include:

- Gender ratio of 50/50 male:female
- US citizen or US Permanent Resident
- Preferred age range of 30 to 55 years
- Height limit of 6’2” maximum
- Professional experience to demonstrate technical skills, including advanced degree or equivalent years of experience
- Demonstrated motivation and work ethic similar to that required by astronauts and astronaut candidates
- Ability to pass the NASA long-duration space flight physical
- Ability to pass psychological assessment by clinical psychologist

The rationale of the above guidelines is to select participants with characteristics similar to those of astronauts to serve as analog astronauts.

Analog astronauts will also be screened for compliance with our exclusion criteria of preexisting sleep problems, sleep apnea, usage of hypnotic medication, diabetes, acute illness, peripheral vascular disease, and major mental disorders. Potential subjects will be administered the Pittsburg Sleep Quality Index to screen for preexisting sleep issues and a questionnaire for the remainder of our exclusion criteria [see Appendix D].

3.4 Recruitment

Our study includes eight separate missions over the course of two years. Applications for HERA analog astronauts are accepted continually via NASA's website. Per NASA protocols, investigators approved to perform research at the HERA facility use these subjects selected by NASA, minimizing the time we require for recruitment. Per NASA protocols, these subjects are also screened for the inclusion and exclusion criteria specified for all research conducted in the HERA facility. All recruitment of subjects for our study will adhere to these guidelines and will fall within the two year timeline required for our proposed research.

3.5 Subject Protection and Confidentiality

There is a long history of human research conducted through NASA and multiple institutional methods of oversight to prevent the exploitation and coercion of potential or actual study participants, as well as safeguards to maintain patient privacy and confidentiality of data. Research conducted on human subjects is guided by the Common Rule, the Belmont Report, and the Declaration of Helsinki.[53] All investigators conducting research that falls under the Common Rule are required to complete a course in ethics training and all studies involving human test subjects require the approval of the Johnson Space Center Institutional Review Board.[31,53] Researchers involved with our project will complete these trainings as well as those required by the Yale University Institutional Review Board for research involving human subjects. Per the protocol for research in the HERA facility, we will work with the NASA Flight Analog Project Scientists to determine the approvals necessary from Yale and to prepare the required protocol submissions to the

Johnson Space Center Institutional Review Board. Appropriate protocol submission forms will be sent to the Yale University Institutional Review Boards for approval.

Due to the nature of the conditions experienced in the HERA facility, human participants would be exposed to isolation, artificial lighting, confinement, a rigorous schedule, and other conditions that may cause physical or psychological distress. All analog astronauts will receive consent briefings by NASA per the administration's protocol for the HERA facility.

The novel intervention proposed here is minimally invasive, requiring only the application of bed socks to the feet. Bed socks are widely available for purchase and use by the public and a previous study utilizing the proposed intervention demonstrated no adverse effects. Although NASA provides a consent briefing for the HERA facility, we will obtain consents specific to our research [see Appendix E] in the 16 days prior to the start of each mission during which we will have access to participants.

All participant data collected over the course of the study will be stored on a secure server. Data will be password-protected and available only to researchers involved in our study. All patient identifying information will be stripped from records and files will be randomly assigned an identification number.

3.6 Methodology Considerations

3.6.1 Constant Routine Protocol

Participants will be subject to the standardized environment, diet, and activity schedules of the HERA facility for the 45 day duration of the study. In addition to these conditions, our study subjects will follow a constant routine protocol prior to lights out, requiring them to

abstain from laying down before 10:55pm, at which time they will get into bed. We will provide subjects with sleepwear consisting of long sleeve T-shirts and sweatpants that will be worn each night for the duration of Period 1 and Period 2 of the study. No additional clothing, including socks other than those worn during the intervention period, will be allowed. Bedding, blankets, and bedsheets will be identical throughout the 45-day duration of the experiment.

3.6.2 Blinding of Intervention

Blinding of participants to their intervention sequence will not be possible since the nature of the intervention involves wearing bed socks. Researchers involved with our study will be blinded to the intervention sequence.

3.6.3 Blinding of Outcomes

Participants will have no access to their objective sleep data during our study but will complete questionnaires evaluating subjective measures of sleep quality and quantity and sleepiness. While it is not possible to blind the subjective outcomes, subjects will be asked to keep their data confidential from other participants and from researchers involved in our study. Researchers will be blinded to outcomes until the conclusion of data collection after the eighth mission.

3.6.4 Assignment of Intervention

Participants for each mission will be randomly assigned to a treatment sequence by computer software in a 1:1 ratio.

3.6.5 Adherence

Adherence to the intervention will be monitored via self-reporting in the daily subjective questionnaire that will be filled out via participants [see Appendix B].

3.6.6 Monitoring of Adverse Events

Monitoring of subjects throughout the duration of their stay in the HERA facility will be provided by the NASA Flight Analogs Team as is standard for HERA operations. Monitoring will occur 24 hours per day, seven days per week. Participants will be informed of protocols for emergency situations prior to their stay in the HERA facility.

3.6.7 Data Collection

Data for the calculation of mean sleep latency, sleep efficiency, total sleep time, and total nightly awakenings will be collected via actigraphy using the Philips Actiwatch Spectrum PRO *(Philips Respironics)*, the equipment available in the HERA facility [see specifications in Appendix F]. Actigraphs will be worn 24 hours a day for the 45 day duration of the study. Although it will not be used in the calculation of our study outcomes, we will collect sleep data for the run-in period to rule out sources of confounding. We will also collect data on movement during waking hours to ensure that activity levels are consistent as anticipated throughout the duration of the study. Participants will be instructed on use of the actigraphs prior to the start of each mission.

Skin temperature data will be collected using the Thermochron iButton [see specifications in Appendix G]. Study participants will be briefed on placement and use of temperature sensors prior to the beginning of the mission. Thermochron iButtons will also be placed in sleeping quarters prior to the beginning of the study to record the ambient temperature to

identify variability in the HERA standard conditions (72 °F +/-5°F) that may introduce potential confounding.

3.6.8 Sample Size Calculation

We based our sample size calculation on objective sleep outcome data from the study by Ko and Lee.[22] Sample sizes were calculated for outcomes of sleep latency, total sleep time, sleep efficiency, and number of awakenings using mean differences of 7.5 minutes, 32 minutes, 7.6%, and 7.5 awakenings and standard deviations of 7.8 minutes, 21.6 minutes, 5.1%, and 4.3 awakenings, respectively. Calculations were made for each of these outcomes using an online software for the calculation of statistical considerations for crossover studies available through the Massachusetts General Hospital Biostatitics Center.[54] We used an alpha of 0.05 and a power of 80% with a two-tailed hypothesis as parameters for our calculation. Calculations using the above data for outcomes of sleep latency, total sleep time, sleep efficiency, and number of awakenings yielded sample sizes of 19, 10, 10, and eight participants. We considered the largest sample size of 19 participants to be the minimum necessary for our study. Given the 32 analog astronauts participating during the HERA campaign, this minimum is feasible and allows for an exclusion or dropout rate of up to 40.6%, or 13 participants. There were no significant outcomes of subjective sleep quality and quantity or sleepiness measures in the research by Ko and Lee available for use in calculation of sample size for our study. However, we chose to include these subjective measures as secondary outcomes in our study both as a tool to validate data collected via actigraphy and to potentially provide useful information for future studies. Given our sample size of 32 participants that is significantly larger than

that of six individuals used in the study by Ko and Lee, it is also possible that our study will be able to detect a significant difference in these outcomes.

The data used for sample size calculation is available in Appendix H.

3.6.9 Analysis

Our study will have the primary outcomes of sleep latency (minutes), total sleep time (minutes), sleep efficiency (percentage), and number of awakenings (total awakenings), all of which will be operationalized as means. Secondary outcomes of our study are subjective measures of sleep quality and quantity and sleepiness and the distal-proximal temperature gradient. We will calculate sleep latency, total sleep time, sleep efficiency, and number of awakenings using participant questionnaires, all of which will be operationalized as means. Subjective ratings of sleep quality and sleepiness will be operationalized as means using a 10 point Likert scale. The distal-proximal temperature gradient (℃) will be operationalized as a mean. Considering that all the outcomes in our study are paired measurements that are continuous, represented as means, and normally distributed, a paired t-test will be used for analysis.

3.6.10 Timeline and Resources

Our study will occur over a period of two years. This time frame includes recruitment, data collection, and statistical analysis. Our study involves eight 45-day missions in the HERA facility (four per year). Astronaut analog selection is made by the NASA Johnson Space Center Test Subject Screening facility per NASA protocol. Data analysis will occur after the conclusion of the final mission.

Our study requires two personnel, a principal investigator and a co-investigator. These individuals will be responsible for traveling to Johnson Space Center during each of the eight pre-mission periods to obtain informed consent and provide briefings on experimental protocols. Our personnel will also be responsible for data analysis at the conclusion of the study. Monitoring of the general conditions of the HERA facility and the well-being of the participants will be provided by the Flight Analogs Team per HERA protocols and does not require personnel supplied by our research team.

Researchers who receive approval for use of the HERA facility are required to provide funding for their research-specific requirements including personnel, equipment not provided in the HERA facility, and research personnel travel. In accordance with these guidelines, we will supply the principal investigator and co-investigator, bed socks, sleepwear, bedding, iButtons, medical tape, and all forms and documents specific to our study.

3.7 References

22. Ko Y, Lee JY. Effects of feet warming using bed socks on sleep quality and thermoregulatory responses in a cool environment. *J Physiol Anthropol.* 2018;37(1):13.
31. NASA. Analog Missions: Want to Participate in HERA? https://www.nasa.gov/analogs/hera/want-to-participate. Published 2018. Accessed 7/13, 2019.
53. NASA. Law/Ethics. https://www.nasa.gov/ames/hrirb/law-ethics. Published 2019. Accessed 7/9, 2019.
54. Schoenfeld D. Statistical considerations for a cross-over study where the outcome is a measurement. http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html. Accessed December 17, 2019.

Chapter 4: Conclusion

4.1 Advantages and Disadvantages

4.1.1 Advantages

There are several advantages of our proposed research. Our intervention, the application of bed socks at bedtime, could provide a novel intervention to prevent and mediate insomnia in astronauts without causing side effects affecting physical or cognitive functioning upon awakening. As previously discussed, crew members are subject to emergent awakenings requiring them to react and perform in potentially life-threatening situations.[3] Unlike the pharmaceutical sleep aids commonly used by astronauts, our intervention has no foreseeable impact on physical or cognitive function. If our study demonstrates a favorable impact of bed socks on sleep, future research could compare their effect on sleep to pharmacologic sleep aids.

A significant consideration in spaceflight is the mass of materials sent to orbit. As previously discussed, given the enormous cost of launching cargo into orbit, the minimal mass of our intervention (approximately 65 grams) is advantageous.[4,47] Further, our intervention is reusable, has a minimal cost at approximately $4 USD/pair bed socks, and is readily available for purchase.[4]

There are also advantages to the use of the HERA facility. While conducting research in spaceflight is ideal, the sample sizes are limited, it is expensive, and the timeline is longer than that of research conducted on Earth.[29] The HERA facility provides an environment on Earth that has proven valuable in sleep research involving applications for spaceflight.[30] Further, while this option is more economical than conducting research in space, it also decreases costs specific to our research due to the availability of equipment including

actigraphy and iPads in the facility, as well as the sharing of the participants and facility personnel among multiple investigations.[27]

4.1.2 Disadvantages

There are some disadvantages to our study. While use of the HERA facility is more feasible than conducting research in spaceflight, participants are not subject to microgravity, a factor known to affect sleep in astronauts. While our study subjects will be exposed to factors such as isolation, confinement, interpersonal stresses, artificial lighting, and schedules similar to those of astronauts on the International Space Station known to affect sleep, the generalizability of our intervention to astronauts may be limited due to the effects of gravity.[5-8] Should our intervention prove effective in analog astronauts, future studies may investigate the use of this intervention in a spaceflight environment.

We were unable to include neurobehavioral testing upon emergent awakening in our study due to the standard light/dark cycles used in the HERA facility and the number of outcomes we are already including in our study. Previous research has demonstrated that zolpidem and zaleplon affect neurobehavioral performance upon emergent awakenings.[3] While prior studies have found no adverse events associated with the wearing of bed socks to improve sleep outcomes, future studies may investigate any potential effects of this intervention on neurobehavioral performance upon emergent awakening, particularly when compared with that of hypnotic medications typically used to prevent sleep.[22]

Our study has a few methodologic limitations that deserve mention. Study subjects cannot be blinded to the intervention, potentially introducing a source of bias. Further, participants cannot be blinded to subjective outcomes, again possibly introducing bias. Participants are also required to apply iButton temperature sensors to their skin at six sites each evening,

possibly introducing a source of error due to variability in placement. While we will attempt to minimize variability by using the mean values from multiple sites to calculate the distal and proximal temperatures, we acknowledge that this may cause confounding.

4.2 Clinical and Public Health Significance

NASA has announced intent to return humans to the moon by 2023 as well as plans to build the Gateway, a permanent lunar orbiting platform, in the near future.[55] These missions, while historic themselves, will serve as a step in the preparation for transit to deep space and a mission to Mars, establishing a human presence farther into space than ever before.[55] Further, with the advent of privatized space exploration through companies such as SpaceX, the number of humans sent to space is only going to grow in the foreseeable future. While we are tackling the logistics of sending humans into the cosmos, we have not yet solved the problem of sleep in space. Our proposed research is relevant not only to the crew members that orbit Earth on the International Space Station, but also to future explorations beyond our home planet.

As more humans are sent into space, there will be an increased need for healthcare providers versed in aerospace medicine who understand the unique set of issues relevant to space travel, including sleep. Physician assistants are already involved in the care of astronaut candidates and crews and are capable of meeting the future medical needs of expanding space exploration. Further, our proposed study has the potential to impact the physical and mental well-being of individuals via improving sleep quality, making our intervention relevant not only to the practice area of aerospace medicine, but for the improvement of patient care on Earth as well. Although our research focuses on the sleep problems affecting astronauts, this nonpharmacological intervention could be applied to

other populations of individuals on Earth that are not ideal candidates for pharmacological sleep aids. Patients such as shift workers, emergency personnel, military personnel, the elderly, or individuals already on multiple medications may benefit from nonpharmacologic sleep interventions in order to minimize adverse effects. Physician assistants familiar with nonpharmacological sleep interventions such as the one proposed here may be better equipped to care for these vulnerable populations.

4.3 References

3. Dinges DF, Basner M, Ecker AJ, Baskin P, Johnston S. Effects of Zolpidem and Zaleplon on Cognitive Performance After Emergent Tmax and Morning Awakenings: a Randomized Placebo-Controlled Trial. *Sleep.* 2018.
4. Gloutique. HASLRA Premium Soft Warm Microfiber Fuzzy Socks 3-5 Pairs. https://gloutique.com/product/haslra-stripe-soft-warm-microfiber-fuzzy-socks-5-pairs-stripe/. Accessed December 17, 2019.
5. Wu B, Wang Y, Wu X, Liu D, Xu D, Wang F. On-orbit sleep problems of astronauts and countermeasures. *Military Medical Research.* 2018;5(1):17.
6. Whitmire A, Leveton L, Barger L, et al. Risk of Performance Errors Due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload Risk of Performance Errors due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload. *Evidence-Based Review by NASA Behavioral Health and Performance Program.* 2009.
7. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *The Lancet Neurology.* 2014;13(9):904-912.
8. Pandi-Perumal SR, Gonfalone AA. Sleep in space as a new medical frontier: the challenge of preserving normal sleep in the abnormal environment of space missions. *Sleep science (Sao Paulo, Brazil).* 2016;9(1):1-4.
22. Ko Y, Lee JY. Effects of feet warming using bed socks on sleep quality and thermoregulatory responses in a cool environment. *J Physiol Anthropol.* 2018;37(1):13.
27. NASA SM. Human Research Program Flight Experiment Information Package. In: Projects ISSM, ed2019.
29. NASA. Human Research Program Human Exploration Research Analog (HERA) Experiment Information Package. In: Program HR, ed2014.
30. NASA. Analog Missions: HERA Research by Campaign. https://www.nasa.gov/analogs/hera/research. Published 2019. Accessed 7/13, 2019.
47. Mosher DaK, S. Here's how much money it actually costs to launch stuff into space. Business Insider. Published 2016. Accessed December 12, 2019.

55. NASA. NASA Unveils Sustainable Campaign to Return to Moon, on to Mars. https://www.nasa.gov/feature/nasa-unveils-sustainable-campaign-to-return-to-moon-on-to-mars. Published 2018. Accessed 7/9, 2019.

Appendices

Appendix A

HERA Subject Daily and Weekly Work Requirements as specified in HERA Facilities and Capabilities Information:

- *"All time spent in the habitat will be working on tasks related to the study.*
- *Subjects awake at 0700 and are off duty at 2300 with one shift operation for all subjects. Sleep period (8.0 hours).*
- *Post-sleep period, includes morning meal (1.5 hours).*
- *Daily planning conferences, medical conferences, work preparation, and plan familiarization (2.0 hours).*
- *Work consists of scheduled research tasks and HERA operations tasks, i.e. HERA maintenance, flight simulator for a spacecraft and/or terrestrial rendezvous mission, public affairs activities, education outreach, etc. (6.5-8.0 hours).*
- *Midday meal (1 hour).*
- *Exercise period (1.25-2.5 hours, includes time for setup, cardiovascular/resistive exercise, stowage, hygiene (cool down and cleanup)).*
- *Pre-sleep period, includes evening meal (2.0 hours).*
- *A nominal 7-day work/rest cycle will consist of 5.5 days available for conducting planned mission tasks and research activities and 1.5 consecutive off-duty days. Housekeeping and 1.0 hour of scheduled work on the weekends is included in the 5.5 working days."* [27]

Appendix B

Daily questionnaire to be completed after awakening.[45,46]

Intervention used last night: Bed socks _____ No intervention _____

How long did it take you to fall asleep after lights out? _____

How many times did you wake up after falling asleep? _____

How many hours of sleep did you get last night? (This may be different than the number of hours spent in bed) _____

What time did you wake up this morning? _____

Please rate the quality of your sleep last night:

1 2 3 4 5 6 7 8 9 10

Poor ⟶ Excellent

Please rate your current level of sleepiness:

1 2 3 4 5 6 7 8 9 10

Cannot stay awake ⟶ Extremely alert

Appendix C

Cuff circumference	16.5 cm
Cuff length	12.0 cm
Foot length	20.0 cm
Fabric thickness	2.4 mm
Mass per area	0.0316 g/cm^2
Air permeability	20.1 $cm^3/cm^2/s$ at 125 hPa
Fabric composition	98.6% polyester, 1.4% polyurethane

Figure 7. Bed sock specifications[22]

Appendix D

The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Component 1	#9 Score	C1_____
Component 2	#2 Score (≤15min=0; 16-30 min=1; 31-60 min=2, >60 min=3) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2_____
Component 3	#4 Score (>7=0; 6-7=1; 5-6=2; <5=3)	C3_____
Component 4	(total # of hours asleep)/(total # of hours in bed) x 100 >85%=0, 75%-84%=1, 65%-74%=2, <65%=3	C4_____
Component 5	Sum of Scores #5b to #5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5_____
Component 6	#6 Score	C6_____
Component 7	#7 Score + #8 Score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7_____

Add the seven component scores together _____ **Global PSQI Score** _____

Figure 6. Pittsburgh Sleep Quality Index.[45] We will use this questionnaire to screen potential study participants. Individuals with a global PSQI score >5 will be excluded from our study.

Screening questionnaire for study participants:

Please check if you have or have ever had the following conditions:

Sleep problems ____

Sleep apnea _____

Use of medications to sleep _____

Diabetes _____

Problems with circulation _____

Mental illness _____

Neurological problems _____

Are you currently ill? Yes _____ No _____

Have you ever been hospitalized? Yes _____ No _____

Do you have any other health problems? Yes _____ No _____

If you answered yes to any questions, please provide further details below:

_____
_____
_____
_____
_____
_____
_____
_____

Appendix E

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 1 (2016-2)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL
NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

Study Title: *Increasing the Distal-Proximal Temperature Gradient with Bed Socks to Improve Sleep Quality and Quantity in Analog Astronauts*

Funding Source: *National Aeronautics and Space Administration, Yale University*

You are invited to participate in a research study designed to look at the ability of socks worn at bedtime to improve sleep in analog astronauts. You have been asked to participate because you submitted an application expressing interest in participating as an analog astronaut in research conducted in the National Aeronautics and Space Administration (NASA) Human Exploration Research Analog (HERA) facility.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Study Location:

Should you decide to participate in this study, you will spend 45 days in confinement with 3 other study subjects in the NASA HERA research facility at the Johnson Space Center in Houston, TX. HERA is a two-story, four-port, 148.1 m^3 closed habitat analog facility designed to simulate conditions associated with time in spaceflight such as isolation, confinement, and remote conditions. You will be quarantined to the facility for the entire duration of the study and will not be permitted regular access to email, phone, or internet.

During your stay in the HERA facility, you will be subject to the following HERA subject daily and weekly work requirements set forth by NASA:

- *All time spent in the habitat will be working on tasks related to the study.*

- *Subjects awake at 0700 and are off duty at 2300 with one shift operation for all subjects. Sleep period (8.0 hours).*
- *Post-sleep period, includes morning meal (1.5 hours).*
- *Daily planning conferences, medical conferences, work preparation, and plan familiarization (2.0 hours).*
- *Work consists of scheduled research tasks and HERA operations tasks, i.e. HERA maintenance, flight simulator for a spacecraft and/or terrestrial rendezvous mission, public affairs activities, education outreach, etc. (6.5-8.0 hours).*
- *Midday meal (1 hour).*
- *Exercise period (1.25-2.5 hours, includes time for setup, cardiovascular/resistive exercise, stowage, hygiene (cool down and cleanup)).*
- *Pre-sleep period, includes evening meal (2.0 hours).*
- *A nominal 7-day work/rest cycle will consist of 5.5 days available for conducting planned mission tasks and research activities and 1.5 consecutive off-duty days. Housekeeping and 1.0 hour of scheduled work on the weekends is included in the 5.5 working days.*

Description of Experimental Procedures:

During your stay in HERA, you will participate in our study, "Increasing the Distal-Proximal Temperature Gradient with Bed Socks to Improve Sleep Quality and Quantity in Analog Astronauts," investigating the impact of socks worn at bedtime on sleep quality and quantity. In addition, you will participate in studies conducted by other research teams for which you will receive separate consent forms.

If you agree to participate in our study, you will take part in both the intervention group [wearing socks at bedtime] and the control group [no socks at bedtime]. You will be randomly assigned via computer software to the order in which you participate in the intervention and control groups. Your participation in the intervention and the control groups will last 15 days for each group. In between your group assignments, there will be an 8 day period during which you participate in neither the intervention or control group. The purpose of this time period is to allow any effects of

the experimental conditions on your sleep to return to baseline. There will also be a 7 day period at the beginning of your stay in HERA during which you will be in neither the intervention or control group. This time period will allow you to adjust to conditions in the HERA facility. You will also take part in a briefing period for 15 days immediately prior to and after the study. You will not be confined to the HERA facility during this time.

Each night you are in the HERA facility, you will wear pajamas provided to you. When assigned to the intervention group, you will put provided socks on one hour prior to lights out each night. Socks will be worn throughout the night and removed at lights on in the morning. While assigned to the control group, you will not be allowed to wear socks or any other items on your feet to bed or for one hour prior to lights out.

Data will be collected via both daily questionnaires and wearable sensors. As a study participant, you will be required to wear an actigraphy watch [similar in size to a wristwatch] that collects information on the movement of your body that is used to calculate how much and how well you sleep. You will also wear temperature sensors [approximately the diameter of a penny] on your forehead, chest, abdomen, thigh, hand, and foot each night while sleeping. Each morning, you will fill out a questionnaire providing information about how much and how well you slept.

Risks and Inconveniences

During your stay in the HERA facility, you will be exposed to conditions such as isolation, confinement, and a rigid schedule that may cause psychological stress. The scheduled daily activities in the HERA facility include physical tasks as well as daily cardiovascular and resistance exercise that may result in physical stress. The HERA facility is monitored 24 hours a day and personnel are available in the case of emergency situations. You will be briefed on emergency procedures should you choose to participate in this study.

Benefits

Studies conducted in the HERA facility are part of NASA's Human Research Program, which funds research to assess effects of long-duration spaceflight on humans, develop and test procedures for optimal astronaut performance, and developing and testing interventions to promote health and performance of astronauts. While the aim of our study is to determine the effects of socks worn at bedtime in improving sleep quality and quantity in analog astronauts, this research may provide information leading to future studies involving the use of the intervention to improve sleep quality and quantity in astronauts in spaceflight. This study will not directly benefit you.

Economic Considerations

You will be provided transportation to and from Johnson Space Center. During your 45 day stay in the HERA facility you will be provided all clothing, food, and supplies necessary for daily living at no cost. In the 15 day briefing periods before and after the study, you will be provided all meals and lodging at no cost to you. You will not be provided any other financial incentives or reimbursements for participating in this study.

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. All participant data collected over the course of this study will be stored on a secure server. Data will be password protected and available only to authorized personnel. All identifying information will be stripped from records and files will be randomly assigned an identification number. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

The HERA facility is equipped with video and audio monitoring in common areas to ensure the safety of study participants in isolation. Sleeping quarters, restrooms, and showers are not monitored. All video and audio recordings will be destroyed at the end of your stay in HERA.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

If you become ill or are physically injured due to participation in this study, you will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by participation in the study will be covered by the Sponsor as long as you have followed the directions of the study doctor.

If you receive a bill for any costs related to the diagnosis or treatment of your injury, please contact the study doctor.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can contact HERA mission control at any time and tell them that you no longer want to take part.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale New Haven Hospital.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

Signature:_____

Relationship:_____

Date:_____

_____ _____
Signature of Principal Investigator Date

or

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator.
If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix F

	Actiwatch 2	Actiwatch Spectrum Plus	Actiwatch Spectrum PRO
Dimensions			
Size	43mm x 23mm x 10 mm	48mm x 37 mm x 15 mm	48mm x 37 mm x 15 mm
Weight	16 grams (with band)	31 grams (with band)	31 grams (with band)
Battery			
Battery type	Lithium rechargeable	Lithium Ion rechargeable	Lithium Ion rechargeable
Typical battery life (at 1 minute epochs, activity and light)	30 days	60 days	50 days (with 4 scores per day)
Memory			
Memory size	1 Mbit	32 Mbits	32 Mbits
Memory volatility	All devices: non volatile		
Recording time			
Recording time (at 1 minute epochs, activity and light)	30 days	60 days	50 days (with 4 scores per day)
Sensors and input specs			
Accelerometer type	Solid state piezo-electric	MEMS type accelerometer	MEMS type accelerometer
Accelerometer sampling rate	32 Hz	32 Hz	32 Hz
Light sensor wavelength range	400-900 nm	400-700 nm	400-700 nm
Light measures	Photopic illuminance	Photopic illuminance Irradiance Photon flux	Photopic illuminance Irradiance Photon flux
Number of scoring items	NA	NA	2 items
Numerical score range	NA	NA	0-15 programmable
Score entry options	NA	NA	Manual or prompted
Environmental attributes			
Moisture protection rating	All devices: *waterproof at 1m for 30 min per IPX7 IEC 60529		
Operating system requirements			
Computer OS compatibility	All devices: Actiware: Windows 8, 7, XP and Vista (32 and 64 bit), Actiware CT: Windows XP Professional; 32 and 64 bit versions of Windows 8 (Professional or Enterprise), 7 (Professional or Ultimate), and Vista (Business or Ultimate)		
Computer hardware	All devices: UL 60950-1, IEC60950-1 or CSA C22.2#60950-1 certified IT equipment, 2 GHz or higher process clock speed, keyboard and mouse, USB port		
USB compatibility	All devices: 2.0 or greater		

Figure 8. Philips Actiwatch specifications [see Actiwatch Spectrum PRO][56]

Appendix G

maxim integrated

DS1921H/DS1921Z
High-Resolution Thermochron iButton Devices

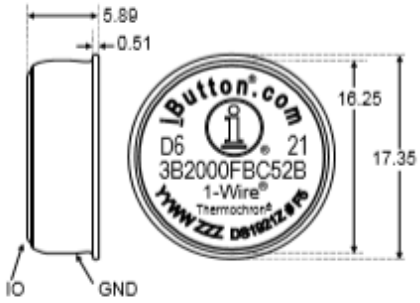
SPECIAL FEATURES

- Digital thermometer measures temperature in 1/8°C increments with ±1°C accuracy
- Built-in real-time clock (RTC) and timer has accuracy of ±2 minutes per month from 0°C to +45°C
- Water resistant or waterproof if placed inside DS9107 iButton® capsule (Exceeds Water Resistant 3 ATM requirements)
- Automatically wakes up and measures temperature at user-programmable intervals from 1 to 255 minutes
- Logs consecutive temperature measurements in 2KB of datalog memory
- Records a long-term temperature histogram with 1/2°C resolution
- Programmable temperature-high and temperature-low alarm trip points
- Records up to 24 time stamps and durations when temperature leaves the range specified by the trip points
- 512 bytes of general-purpose battery-backed SRAM
- Communicates to host with a single digital signal at 15.4kbits or 125kbits per second using 1-Wire® protocol
- Fixed range: H: +15°C to +46°C; Z: -5°C to +26°C

COMMON iButton DEVICE FEATURES

- Digital identification and information by momentary contact
- Unique, factory-lasered and tested 64-bit registration number (8-bit family code + 48-bit serial number + 8-bit CRC tester) assures absolute traceability because no two parts are alike
- Multidrop controller for 1-Wire net
- Chip-based data carrier compactly stores information
- Data can be accessed while affixed to object
- Button shape is self-aligning with cup-shaped probes
- Durable stainless steel case engraved with registration number withstands harsh environments
- Easily affixed with self-stick adhesive backing, latched by its flange, or locked with a ring pressed onto its rim
- Presence detector acknowledges when reader first applies voltage

PIN CONFIGURATION



All dimensions are shown in millimeters.

ORDERING INFORMATION

PART	TEMP RANGE	PIN-PACKAGE
DS1921H-F5#	+15°C to +46°C	F5 Can
DS1921Z-F5#	-5°C to +26°C	F5 Can

#Denotes a RoHS-compliant device that may include lead(Pb) that is exempt under the RoHS requirements.

EXAMPLES OF ACCESSORIES

DS9096P	Self-Stick Adhesive Pad
DS9101	Multi-Purpose Clip
DS9093RA	Mounting Lock Ring
DS9093A	Snap-In Fob
DS9092	iButton Device Probe

Figure 9. Thermochron iButton specifications.[57]

Appendix H

Alpha	0.05
Power	80%
Hypothesis	Two-tailed
Sleep latency[22]	7.5 min, SD = 7.8 min
Total sleep time[22]	32 min, SD = 21.6 min
Sleep efficiency[22]	7.6 %, SD = 5.1%
Number of awakenings[22]	7.5 awakenings, SD = 4.3 awakenings

Figure 10. Data used for sample size calculation.

Appendix: References:

22. Ko Y, Lee JY. Effects of feet warming using bed socks on sleep quality and thermoregulatory responses in a cool environment. *J Physiol Anthropol.* 2018;37(1):13.
27. NASA SM. Human Research Program Flight Experiment Information Package. In: Projects ISSM, ed2019.
45. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 1989;28(2):193-213.
46. Kaida K, Takahashi M, Akerstedt T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2006;117(7):1574-1581.
56. Philips K. Professional sleep and activity monitoring solutions: Specifications for Actiwatch 2, Actiwatch Spectrum Plus, and Actiwatch Spectrum PRO. In:2013.
57. iButtonLink L. DS 192 1H-F5 Thermochron high res 15 to 46 C. https://www.ibuttonlink.com/products/ds1921h. Published 2020. Accessed March 31, 2020.

Bibliography:

1. Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National use of prescription medications for insomnia: NHANES 1999-2010. *Sleep.* 2014;37(2):343-349.
2. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: AN observational study. *Lancet Neurol.* 2014;13(9):904-912.
3. Dinges DF, Basner M, Ecker AJ, Baskin P, Johnston S. Effects of Zolpidem and Zaleplon on Cognitive Performance After Emergent Tmax and Morning Awakenings: a Randomized Placebo-Controlled Trial. *Sleep.* 2018.
4. Gloutique. HASLRA Premium Soft Warm Microfiber Fuzzy Socks 3-5 Pairs. https://gloutique.com/product/haslra-stripe-soft-warm-microfiber-fuzzy-socks-5-pairs-stripe/. Accessed December 17, 2019.
5. Wu B, Wang Y, Wu X, Liu D, Xu D, Wang F. On-orbit sleep problems of astronauts and countermeasures. *Military Medical Research.* 2018;5(1):17.
6. Whitmire A, Leveton L, Barger L, et al. Risk of Performance Errors Due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload Risk of Performance Errors due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload. *Evidence-Based Review by NASA Behavioral Health and Performance Program.* 2009.
7. Barger LK, Flynn-Evans EE, Kubey A, et al. Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *The Lancet Neurology.* 2014;13(9):904-912.
8. Pandi-Perumal SR, Gonfalone AA. Sleep in space as a new medical frontier: the challenge of preserving normal sleep in the abnormal environment of space missions. *Sleep science (Sao Paulo, Brazil).* 2016;9(1):1-4.
9. Brainard GC, Barger LK, Soler RR, Hanifin JP. The development of lighting countermeasures for sleep disruption and circadian misalignment during spaceflight. *Curr Opin Pulm Med.* 2016;22(6):535-544.
10. Flynn-Evans EE, Barger LK, Kubey AA, Sullivan JP, Czeisler CA. Circadian misalignment affects sleep and medication use before and during spaceflight. *npj Microgravity.* 2016;2.
11. Gregory K. *Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload.* 2016.
12. Wotring VE. Medication use by U.S. Crewmembers on the International space station. *FASEB J.* 2015;29(11):4417-4423.
13. Troynikov O, Watson CG, Nawaz N. Sleep environments and sleep physiology: A review. *J Therm Biol.* 2018;78:192-203.
14. Krauchi K, Cajochen C, Werth E, Wirz-Justice A. Warm feet promote the rapid onset of sleep. *Nature.* 1999;401(6748):36-37.
15. Abe N, Kodama H. Distal-proximal skin temperature gradient prior to sleep onset in infants for clinical use. *Pediatr Int.* 2015;57(2):227-233.

16. McCabe SM, Elliott C, Langdon K, Abbiss CR. Patterns and reliability of children's skin temperature prior to and during sleep in the home setting. *Physiology & behavior.* 2018;194:292-301.
17. Ichiba T, Suzuki M, Aritake-Okada S, Uchiyama M. Periocular skin warming elevates the distal skin temperature without affecting the proximal or core body temperature. *Scientific reports.* 2019;9(1):5743.
18. Sung EJ, Tochihara Y. Effects of bathing and hot footbath on sleep in winter. *Journal of physiological anthropology and applied human science.* 2000;19(1):21-27.
19. Liao WC, Landis CA, Lentz MJ, Chiu MJ. Effect of foot bathing on distal-proximal skin temperature gradient in elders. *International journal of nursing studies.* 2005;42(7):717-722.
20. Liao WC, Chiu MJ, Landis CA. A warm footbath before bedtime and sleep in older Taiwanese with sleep disturbance. *Research in nursing & health.* 2008;31(5):514-528.
21. Oshima-Saeki C, Taniho Y, Arita H, Fujimoto E. Lower-limb warming improves sleep quality in elderly people living in nursing homes. *Sleep Sci.* 2017;10(2):87-91.
22. Ko Y, Lee JY. Effects of feet warming using bed socks on sleep quality and thermoregulatory responses in a cool environment. *J Physiol Anthropol.* 2018;37(1):13.
23. Krauchi K, Cajochen C, Wirz-Justice A. Waking up properly: is there a role of thermoregulation in sleep inertia? *Journal of sleep research.* 2004;13(2):121-127.
24. Dorsey CM, Lukas SE, Teicher MH, et al. Effects of passive body heating on the sleep of older female insomniacs. *Journal of geriatric psychiatry and neurology.* 1996;9(2):83-90.
25. NASA. Human Research Program: About International Space Station Medical Projects. https://www.nasa.gov/hrp/elements/issmp/about. Published 2018. Accessed 7/12, 2019.
26. NASA. Human Exploration Research Opportunities (HERO). In:2017.
27. NASA SM. Human Research Program Flight Experiment Information Package. In: Projects ISSM, ed2019.
28. NASA. Analog Missions. https://www.nasa.gov/analogs/hera. Published 2019. Accessed 7/13, 2019.
29. NASA. Human Research Program Human Exploration Research Analog (HERA) Experiment Information Package. In: Program HR, ed2014.
30. NASA. Analog Missions: HERA Research by Campaign. https://www.nasa.gov/analogs/hera/research. Published 2019. Accessed 7/13, 2019.
31. NASA. Analog Missions: Want to Participate in HERA? https://www.nasa.gov/analogs/hera/want-to-participate. Published 2018. Accessed 7/13, 2019.
32. Stoner J. Cross-Over Trials in Clinical Research (2nd ed.) by Stephen Senn. *Journal of the American Statistical Association.* 2004;99.
33. Martin JL, Hakim AD. Wrist actigraphy. *Chest.* 2011;139(6):1514-1527.

34. Izmailova ES, McLean IL, Bhatia G, et al. Evaluation of Wearable Digital Devices in a Phase I Clinical Trial. *Clin Transl Sci.* 2019;12(3):247-256.
35. Kramer NaM, R. Overview of polysomnography in adults. UpToDate. Published 2018. Updated September 11, 2018. Accessed December 13, 2019.
36. Monk TH, Buysse DJ, Rose LR. Wrist actigraphic measures of sleep in space. *Sleep.* 1999;22(7):948-954.
37. Basner M, Dinges DF, Mollicone D, et al. Mars 520-d mission simulation reveals protracted crew hypokinesis and alterations of sleep duration and timing. *Proceedings of the National Academy of Sciences of the United States of America.* 2013;110(7):2635-2640.
38. Hasselberg MJ, McMahon J, Parker K. The validity, reliability, and utility of the iButton(R) for measurement of body temperature circadian rhythms in sleep/wake research. *Sleep medicine.* 2013;14(1):5-11.
39. van Marken Lichtenbelt WD, Daanen HA, Wouters L, et al. Evaluation of wireless determination of skin temperature using iButtons. *Physiology & behavior.* 2006;88(4-5):489-497.
40. Smith AD, Crabtree DR, Bilzon JL, Walsh NP. The validity of wireless iButtons and thermistors for human skin temperature measurement. *Physiological measurement.* 2010;31(1):95-114.
41. Sarabia JA, Rol MA, Mendiola P, Madrid JA. Circadian rhythm of wrist temperature in normal-living subjects A candidate of new index of the circadian system. *Physiology & behavior.* 2008;95(4):570-580.
42. Rutkove SB, Nie R, Mitsa T, Nardin RA. A methodology for the real-time measurement of distal extremity temperature. *Physiological measurement.* 2007;28(11):1421-1428.
43. Raymann RJ, Swaab DF, Van Someren EJ. Cutaneous warming promotes sleep onset. *American journal of physiology Regulatory, integrative and comparative physiology.* 2005;288(6):R1589-1597.
44. Fronczek R, Raymann RJ, Romeijn N, et al. Manipulation of core body and skin temperature improves vigilance and maintenance of wakefulness in narcolepsy. *Sleep.* 2008;31(2):233-240.
45. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 1989;28(2):193-213.
46. Kaida K, Takahashi M, Akerstedt T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2006;117(7):1574-1581.
47. Mosher DaK, S. Here's how much money it actually costs to launch stuff into space. Business Insider. Published 2016. Accessed December 12, 2019.
48. Thurman SM, Wasylyshyn N, Roy H, et al. Individual differences in compliance and agreement for sleep logs and wrist actigraphy: A longitudinal study of naturalistic sleep in healthy adults. *PloS one.* 2018;13(1):e0191883-e0191883.
49. Taibi DM, Landis CA, Vitiello MV. Concordance of polysomnographic and actigraphic measurement of sleep and wake in older women with insomnia. *J Clin Sleep Med.* 2013;9(3):217-225.

50. Smith MT, McCrae CS, Cheung J, et al. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. *J Clin Sleep Med.* 2018;14(7):1209-1230.
51. Cellini N, Buman MP, McDevitt EA, Ricker AA, Mednick SC. Direct comparison of two actigraphy devices with polysomnographically recorded naps in healthy young adults. *Chronobiol Int.* 2013;30(5):691-698.
52. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. Before-bedtime passive body heating by warm shower or bath to improve sleep: A systematic review and meta-analysis. *Sleep medicine reviews.* 2019;46:124-135.
53. NASA. Law/Ethics. https://www.nasa.gov/ames/hrirb/law-ethics. Published 2019. Accessed 7/9, 2019.
54. Schoenfeld D. Statistical considerations for a cross-over study where the outcome is a measurement. http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html. Accessed December 17, 2019.
55. NASA. NASA Unveils Sustainable Campaign to Return to Moon, on to Mars. https://www.nasa.gov/feature/nasa-unveils-sustainable-campaign-to-return-to-moon-on-to-mars. Published 2018. Accessed 7/9, 2019.
56. Philips K. Professional sleep and activity monitoring solutions: Specifications for Actiwatch 2, Actiwatch Spectrum Plus, and Actiwatch Spectrum PRO. In:2013.
57. iButtonLink L. DS 192 1H-F5 Thermochron high res 15 to 46 C. https://www.ibuttonlink.com/products/ds1921h. Published 2020. Accessed March 31, 2020.